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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,989	12/23/2005	Philippe Guedat	MERCK-3095	3186

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EXAMINER	
CHANG, CELIA C	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
02/04/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,989	GUEDAT ET AL.	
	Examiner	Art Unit	
	Celia Chang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *9 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-8, 10-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group I, species of compound 38, p.46 in the reply filed on Oct. 16, 2008 is acknowledged. The traversal is on the ground that the patent office has not established that there would be undue burden to search all. This is not found persuasive because as it was clearly delineated in the restriction requirement that the "R1" moiety must be included as the core structure because :

i) when R1 is sbustituted alkyl, A is a2m R2/R3 are noncyclic, the compound is classified in class 546/209, such compounds have anti-tumor activity (Haupt et al. CA124:33070);

ii) when R1 is substituted phenyl, one of R2/R3 is phenyl, the compound is classified in class 546/210, such compounds are useful in treating liver and pancrease disease (Otte et al. CA 147:344079);

iii) when R1 is heteroaryl, one of R2/R3 is heteroaryl, the compound is classified in class 544/269, such compounds are NF-κB signaling inhitors (Leban et al. CA 147:479784);

iv) when R1 is biphenyl, one of R2/R3 is substituted phenyl, the compound is classified in class 544/360, such compounds are trkA receptor inhibitors (Sugasawa et al. CA 147:502346).

These are sample searches corresponding to limited R1 variable. The enormous burden on the office were restriction not made is self evident. In addition, each core is corresponding to a different utility, thus, the non-coextensive nature is well recognized.

The requirement is still deemed proper and is therefore made FINAL.

Based on the election, claims 10 and 15 and claims 1-8, 11-14, 16-17 reading on R1 is biphenyl, A is a2 and R2 and R3 do not form a ring are prosecuted. Claims 9, 18 and the remaining subject matter of claims 1-8, 11-14, 16-17 are withdrawn from consideration per 37 CFR 1.142(b).

2. Claims 1-8, 11-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, the claims recite the broad recitation in Markush elements, and the claim also recites "especially" or "preferably" selection among the Markush variations which is the narrower statement of the range/limitation.

It is recommended, the explicit moieties be listed with deletion of the "especially" or "preferred" terms and choices.

3. Claims 1-8, 10-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The scope of the claims being drawn to "solvates" "hydrates" or "prodrugs" of the compounds lacks sufficient support as to what they are and how they are made.

The specification gave no definition of what kind of solvates i.e. with what solvents, or hydrates i.e. hemi-, mono-, di-…etc. or what is a prodrug as to offer any meets and bounds of the scope. It is clearly stated by one having ordinary skill in the art that in the event of solvates (for which hydrates is included), "*One can say that if the formation of polymorphs is a nuisance for crystal engineers, solvate formation can be a nightmare, because it is extremely difficult to* ***predict*** *whether anew species may crystallizes from solution with one or more molecules of solvent*" (see p.3940, right column). In absence of any guidance on which solvents, with which compound, or any condition and availability of any solvates or hydrates, the specification lacks

sufficient enablement of the scope as claimed. While formula I containg organic base is operable in forming pharmaceutically acceptable salts with pharmaceutically acceptable acid, such compound per se does not provide enablement for all solvates, hydrates which are different chemical entity from compound per se.

The specification provided no information as to which prodrug or what functional group of the compounds of formula I would meet the "prodrug" modification requirement. As it was well recognized in the pharmaceutical art, prodrugs are modification of an active drug and to qualify for a prodrug, the modified compound must be inactive and is activated by the metabolic system (see Prodrug definition from the Web). No toxicity information, bioavalability/solubility information etc. were disclosed in the specification as to enable one having ordinary skill to warrant the scope of unlimited prodrugs.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

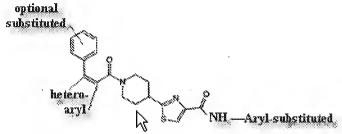
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-8, 10-14, 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knox et al. US 2006/0135501.

Knox et al. '501 is prior art because the effective filing dated is Dec. 24, 2002 corresponding to GB0230162.0.

Determination of the scope and content of the prior art (MPEP §2141.01)

The Knox et al. '501 generically disclosed the instantly claimed compounds as seen in the two species delineated on p.19, compound 1506-00404 and p.22 compound 1506-08722 which had the following structure:



wherein the heteroaryl moiety for 1506-00404 is isoxazol and for 1506-08722 is diazol.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The instant *elected species* is that the heteroaryl moiety is a phenyl/aryl group, thus, differ from the above species in that instead of a heteroaryl, it is an aryl group. Generically, Knox et al. disclosed that W is optionally an aryl substituted aryl or unsaturated heterocyclic moieties (see p.2 W definition and p. 3 [0028] and [0029] optional substituents including phenyl); thus, the optional choices of the instant biphenyl and the exemplified heteoraryl-phenyl compounds.

Finding of prima facie obviousness---rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art in possession of the Knox et al. reference is in possession of the instant claims because the generic teaching guided by the particular exemplification provided guidance in picking and choosing among the various Markush elements. In absence of unexpected results, there is nothing unobvious in picking some among many. In re Lemin 141 USPQ 814. On e would expect all the compounds embraced by the generic formula would have the disclosed utility i.e. treating dislipidimia etc.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

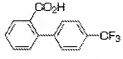
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-8, 10-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knox et al. US 2006/0135501 in view of Dupuis et al.

The rational of finding the generic claims prima facie obvious has been delineated supra and hereby incorporated by reference.

The limitation of the species of claim 15 wherein the optional substituent on the phenyl ring of the biphenyl moiety being trifluoromethyl is further prima facie obvious in view of Dupuis et al.

Knox et al. disclosed that for compounds of formula I or II, wherein q=0 (see p.2), the process of making requires the $R1CO_2H$ starting material (see p.112 scheme 2 process making (5)-6a-e). For making of the instantly elected trifluoromethyl substituted biphenyl, the $R1CO_2H$ starting material would be:



Dupuis et al. provided the starting material source readily available to one having ordinary skill. Therefore, the elected trifluoromethyl substitution would be prima facie obvious over the unsubstituted examples of the Knox et al. which disclosed CF3 as an optional substituents. One having ordinary skill would favorably pick the optional CF3 substitution in view of the readily available starting material.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang, Ph. D. whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres, Ph. D., can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

OACS/Chang
Jan. 29, 2009

/Celia Chang/
Primary Examiner
Art Unit 1625